ANDA 74-661

L. Perrigo Company
Attention: Jacqueline M. Eaton
117 Water Street
Allegan, Michigan 49010

Dear Madam:

This is in reference to your abbreviated new drug application dated April 24, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Naproxen Sodium Tablets USP, 220 mg (eq. 200 mg base), round and capsule-shaped tablets.

Reference is also made to our letter dated October 3, 1996 granting tentative approval to this abbreviated application and to your amendment dated October 9, 1996.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted Over-The-Counter (OTC) labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Naproxen Sodium Tablets USP 220 mg (eq. 200 mg base) to be bioequivalent to the listed drug, Aleve Tablets 220 mg (eq. 200 mg base) of Hamilton Pharmaceuticals Ltd. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Sincerely yours,

1/13/97

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

ANDA 74-661

Perrigo Company
Attention: Jacqueline M. Eaton
117 Water Street
Allegan, MI 49010

Dear Madam:

This is in reference to your abbreviated new drug application dated April 24, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Naproxen Sodium Tablets USP, 220 mg (eq. 200 mg base), round and capsule-shaped tablets.

Reference is also made to your amendments dated May 11 and December 14, 1995, and August 27 and September 4, 1996.

We have completed the review of this abbreviated application and have concluded that based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is **tentatively approved.** This determination is contingent upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product), and is therefore subject to change on the basis of new information that may come to our attention. The listed reference drug upon which you have based your application is subject to a period of market exclusivity and therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(4)(D) of the Act until the period has expired, i.e., January 11, 1997.

Please provide the Agency, at least 60 days prior to January 11, 1997, an amendment to this application. This amendment should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should also be submitted even if none of these changes were made. This submission should be designated as a MINOR AMENDMENT in your cover letter. In addition to, or instead of, the amendment requested above, the Agency may, at any time prior to the final date of approval, request that you submit an amendment containing the information described above. Failure to submit such an amendment requested by the Agency will prompt a review of the application which may result in rescission of this tentative approval letter.

Any significant changes in the conditions outlined in this abbreviated application require Agency approval before the changes may be made effective.

Prior to issuance of a final approval letter by the Agency, your product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list, alternatively known as the "Orange Book", published by the Agency. Should you believe that there are grounds for our issuance of a final approval letter prior to January 11, 1997, you should amend your application accordingly.

At the time you submit any amendments, you should contact Mr. James Wilson, Project Management Officer, at (301) 594-0310, for further instructions.

The introduction or delivery for introduction into interstate commerce of the drug product before the effective approval date is prohibited under 21 U.S.C. 331(d).

Sincerely yours,

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

FINAL PRINTED LABELING
ANDA #74-661
Tablet, 24 Count Label & Carton

FINAL PRINTED LABELING
ANDA #74-661
Tablet, 400 Count Label

Now In *NON-PRESCRIPTION* Strength
FAST, LONG-LASTING PAIN RELIEF

Naproxen Sodium

TABLETS, USP

PAIN RELIEVER / FEVER REDUCER

WITH 8 TO 12 HOUR DOSING

DO NOT USE IF PRINTED SEAL ON BOTTLE OPENING IS MISSING OR BROKEN

COMPARE TO ALEVE®'S ACTIVE INGREDIENT

400 TABLETS 220 MG EACH

ALLERGY WARNING: Do not take this product if you have had either hives or a severe allergic reaction after taking any pain reliever. Even though this product may not contain the same ingredient, Naproxen Sodium could cause similar reactions in patients allergic to other pain relieving drugs.
ALCOHOL WARNING: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Naproxen Sodium and other pain relievers.
INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever.
GENERAL WARNINGS: Do not take naproxen sodium tablets for more than 10 days for pain, or for more than 3 days for fever, unless directed by a doctor.
Consult a doctor if:
- your pain or fever persists or gets worse
- the painful area is red or swollen
- you take any other drugs on a regular basis
- you have had serious side effects from any pain reliever
- you have any new or unusual symptoms
- more than mild heartburn, upset stomach, or stomach pain occurs with use of this product or if even mild symptoms persist

Although naproxen sodium is indicated for the same conditions as aspirin, ibuprofen and acetaminophen, it should not be taken with them or other naproxen-containing products except under a doctor's direction. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE NAPROXEN SODIUM DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.
Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.
Store at room temperature; avoid excessive heat 40°C (104°F).
DIRECTIONS: Adults: Take 1 tablet every 8 to 12 hours while symptoms persist. With experience, some people may find that an initial dose of 2 tablets followed by 1 tablet 12 hours later, if necessary, will give better relief. *Do not exceed 3 tablets in 24 hours unless directed to do so by a doctor.* The smallest effective dose should be used. A full glass of water or other liquid is recommended with each dose.
Adults over age 65: Do not take more than 1 tablet every 12 hours, unless directed to do so by a doctor.
Children under age 12: Do not give this product to children under 12, except under the advice and supervision of a doctor.
Active Ingredient: Each tablet contains naproxen sodium 220 mg (naproxen 200 mg and sodium 20 mg).
Inactive Ingredients: Carnauba Wax, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Povidone, Talc, Titanium Dioxide.

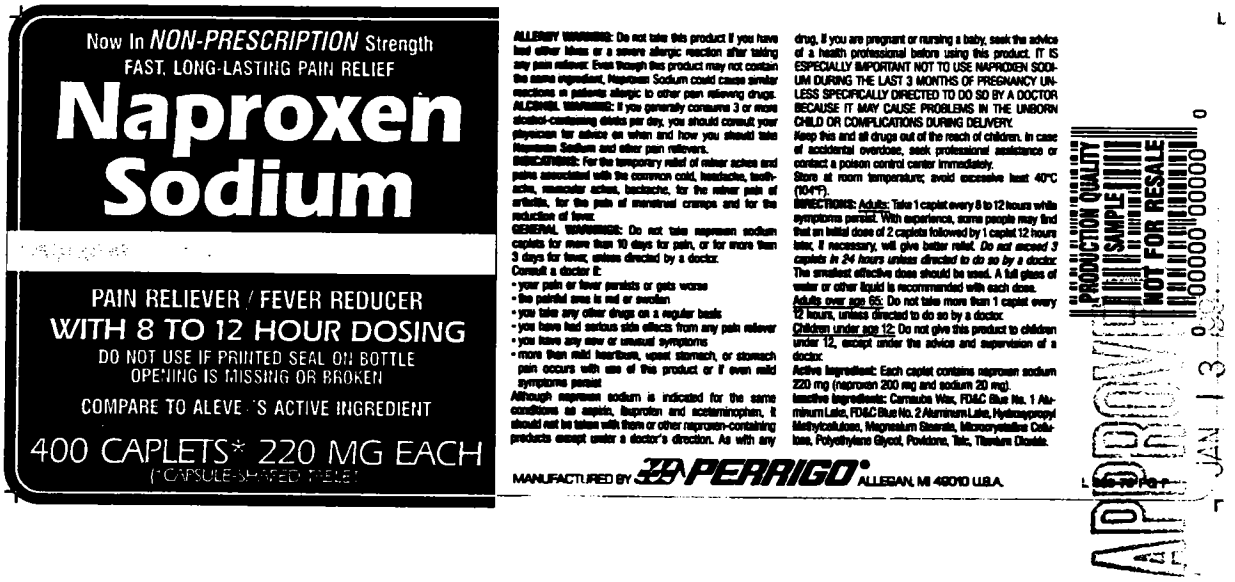
MANUFACTURED BY PERRIGO ALLEGAN, MI 49010 U.S.A.

JAN 13 1997

L 490 75 PG F

PRODUCTION QUALITY SAMPLE NOT FOR RESALE

FINAL PRINTED LABELING
ANDA #74-661
Caplet, 400 Count Label



Now In *NON-PRESCRIPTION* Strength
FAST, LONG-LASTING PAIN RELIEF

Naproxen Sodium

PAIN RELIEVER / FEVER REDUCER
WITH 8 TO 12 HOUR DOSING
DO NOT USE IF PRINTED SEAL ON BOTTLE OPENING IS MISSING OR BROKEN
COMPARE TO ALEVE® S ACTIVE INGREDIENT
400 CAPLETS* 220 MG EACH
(*CAPSULE-SHAPED TABLET)

ALLERGY WARNING: Do not take this product if you have had either hives or a severe allergic reaction after taking any pain reliever. Even though this product may not contain the same ingredient, Naproxen Sodium could cause similar reactions in patients allergic to other pain relieving drugs.
ALCOHOL WARNING: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Naproxen Sodium and other pain relievers.
DESCRIPTION: For the temporary relief of minor aches and pains associated with the common cold, headache, toothache, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever.
GENERAL WARNINGS: Do not take naproxen sodium caplets for more than 10 days for pain, or for more than 3 days for fever, unless directed by a doctor.
Consult a doctor if:
- your pain or fever persists or gets worse
- the painful area is red or swollen
- you take any other drugs on a regular basis
- you have had serious side effects from any pain reliever
- you have any new or unusual symptoms
- more than mild heartburn, upset stomach, or stomach pain occurs with use of this product or if even mild symptoms persist

Although naproxen sodium is indicated for the same conditions as aspirin, ibuprofen and acetaminophen, it should not be taken with them or other naproxen-containing products except under a doctor's direction. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE NAPROXEN SODIUM DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.
Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.
Store at room temperature; avoid excessive heat 40°C (104°F).
DIRECTIONS: Adults: Take 1 caplet every 8 to 12 hours while symptoms persist. With experience, some people may find that an initial dose of 2 caplets followed by 1 caplet 12 hours later, if necessary, will give better relief. *Do not exceed 3 caplets in 24 hours unless directed to do so by a doctor.* The smallest effective dose should be used. A full glass of water or other liquid is recommended with each dose.
Adults over age 65: Do not take more than 1 caplet every 12 hours, unless directed to do so by a doctor.
Children under age 12: Do not give this product to children under 12, except under the advice and supervision of a doctor.
Active Ingredient: Each caplet contains naproxen sodium 220 mg (naproxen 200 mg and sodium 20 mg).
Inactive Ingredients: Carnauba Wax, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Povidone, Talc, Titanium Dioxide.

MANUFACTURED BY PERRIGO ALLEGAN, MI 49010 U.S.A.

PRODUCTION QUALITY SAMPLE NOT FOR RESALE

APPROVED JAN 13 2003

FINAL PRINTED LABELING
ANDA #74-661
Caplet, 24 Count Label & Carton

Naproxen Sodium CAPLETS

PAIN RELIEVER / FEVER REDUCER

ALLERGY WARNING: Do not take this product if you have had either hives or a severe allergic reaction after taking any pain reliever. Even though this product may not contain the same ingredient, Naproxen Sodium could cause similar reactions in patients allergic to other pain relieving drugs.

ALCOHOL WARNING: If you generally consume 3 or more alcohol-containing drinks per day, you should consult your physician for advice on when and how you should take Naproxen Sodium and other pain relievers.

INDICATIONS: For the temporary relief of minor aches and pains associated with the common cold, headaches, toothaches, muscular aches, backache, for the minor pain of arthritis, for the pain of menstrual cramps and for the reduction of fever.

GENERAL WARNINGS: Do not take naproxen sodium caplets for more than 10 days for pain, or for more than 3 days for fever, unless directed by a doctor. Consult a doctor if:

- your pain or fever persists or gets worse
- the painful area is red or swollen
- you take any other drugs on a regular basis
- you have had serious side effects from any pain reliever
- you have any new or unusual symptoms
- more than mild heartburn, upset stomach, or stomach pain occurs with use of this product or if these mild symptoms persist.

Although naproxen sodium is indicated for the same conditions as aspirin, ibuprofen and acetaminophen, it should not be taken with them or other naproxen-containing products except under a doctor's direction. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product. IT IS ESPECIALLY IMPORTANT NOT TO USE NAPROXEN SODIUM DURING THE LAST 3 MONTHS OF PREGNANCY UNLESS SPECIFICALLY DIRECTED TO DO SO BY A DOCTOR BECAUSE IT MAY CAUSE PROBLEMS IN THE UNBORN CHILD OR COMPLICATIONS DURING DELIVERY.

Keep this and all drugs out of the reach of children. In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

Store at room temperature; avoid excessive heat 40°C (104°F).

DIRECTIONS: Adults: Take 1 caplet every 8 to 12 hours while symptoms persist. With experience, some people may find that an initial dose of 2 caplets followed by 1 caplet 12 hours later, if necessary, will give better relief. *Do not exceed 3 caplets in 24 hours unless directed to do so by a doctor.* The smallest effective dose should be used. A full glass of water or other liquid is recommended with each dose.

Adults over age 65: Do not take more than 1 caplet every 12 hours, unless directed to do so by a doctor.

Children under age 12: Do not give this product to children under 12, except under the advice and supervision of a doctor.

Active Ingredient: Each caplet contains naproxen sodium 220 mg (naproxen 200 mg and sodium 20 mg).

Inactive Ingredients: Carnauba Wax, FD&C Blue No. 1 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, Hydroxypropyl Methylcellulose, Magnesium Stearate, Microcrystalline Cellulose, Polyethylene Glycol, Povidone, Talc, Titanium Dioxide.

MANUFACTURED BY
PERRIGO®
ALLEGAN, MI 49010 U.S.A.

EXP.
LOT NO.
3 368 62 PQ A
SAMPLE
PRODUCTION QUALITY
NOT FOR RESALE

Now In *NON-PRESCRIPTION* Strength
FAST, LONG-LASTING PAIN RELIEF
Naproxen Sodium

PAIN RELIEVER / FEVER REDUCER
WITH 8 TO 12 HOUR DOSING
COMPARE TO ALEVE ® S ACTIVE INGREDIENT
24 CAPLETS* 220 MG EACH

Naproxen Sodium

PAIN RELIEVER FEVER REDUCER
WITH 8 TO 12 HOUR DOSING
DO NOT USE IF CARTON IS OPEN OR IF PRINTED SEAL ON BOTTLE OPENING IS MISSING OR BROKEN.
READ CONSUMER LEAFLET BEFORE USE.

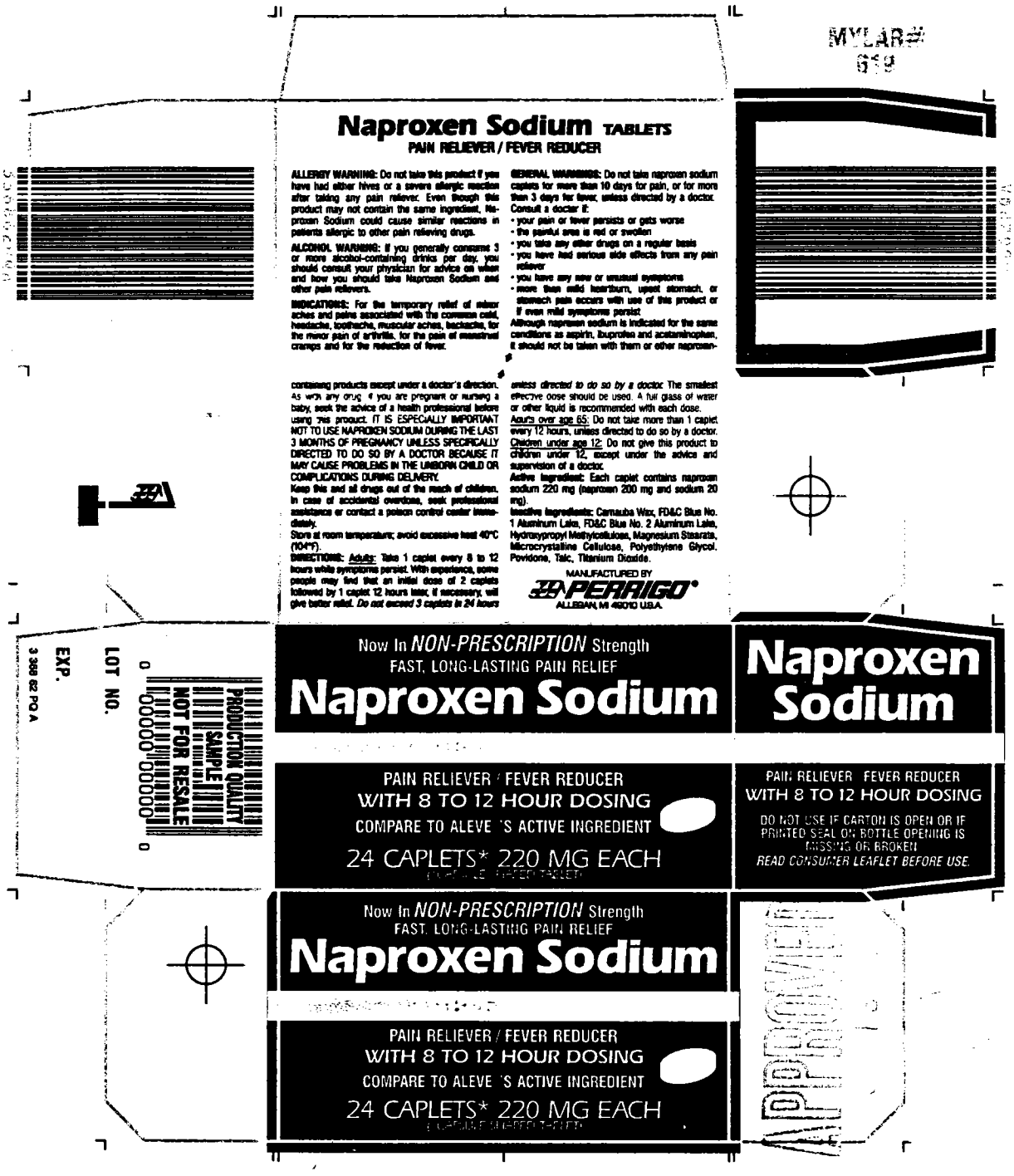
Now In *NON-PRESCRIPTION* Strength
FAST, LONG-LASTING PAIN RELIEF
Naproxen Sodium

PAIN RELIEVER FEVER REDUCER
WITH 8 TO 12 HOUR DOSING
COMPARE TO ALEVE ® S ACTIVE INGREDIENT
24 CAPLETS* 220 MG EACH

Naproxen Sodium

PAIN RELIEVER FEVER REDUCER
WITH 8 TO 12 HOUR DOSING
24 CAPLETS* 220 MG EACH

FINAL PRINTED LABELING
ANDA #74-661
Caplet, 24 count Carton



1. CHEMISTRY REVIEW NO 4

2. ANDA 74-661

3. NAME AND ADDRESS OF APPLICANT
Perrigo Company
Attention: Jacqueline M. Eaton
117 Water Street
Allegan, MI 49010

4. LEGAL BASIS FOR SUBMISSION See next page.

5. SUPPLEMENT(s) N/A 6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Naproxen Sodium Tablets, USP

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES: See next page.

10. PHARMACOLOGICAL CATEGORY NSAID 11. Rx or OTC OTC

12. RELATED IND/NDA/DMF(s)

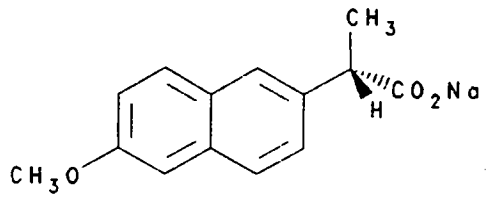
13. DOSAGE FORM
Tablets

14. POTENCY
220 mg (eq. 200 mg base)

15. CHEMICAL NAME AND STRUCTURE
(-)-Sodium 6-methoxy-α-methyl-2-naphthaleneacetate

$C_{14}H_{13}NaO_3$ Mol. wt. = 252.24

[26159-34-2]



16. RECORDS AND REPORTS N/A

17. COMMENTS No changes reported since tentative approval.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: APPROVAL.

19. REVIEWER: J. L. Smith DATE COMPLETED: 01/10/97

cc: 74-661
DUP Jacket
Division File

Endorsements:
HFD-623/J.Smith 1/10/97
HFD-623/V.Sayeed, Ph.D. /ATL/ 1-10-97
Y:\NEW\FIRMSNZ\PERRIGO\LTRS&REV\74661AP4.C
F/T by:

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/AADA # 74-661 SPONSOR: Perrigo Company
DRUG: Naproxen Sodium
DOSAGE FORM: Tablets / Caplets
STRENGTH(s): 220 mg
TYPE OF STUDY: Single/~~Multiple~~ Fasting/Fed
STUDY SITE:

STUDY SUMMARY: The bioequivalence studies under fasting and nonfasting conditions conducted on Naproxen Sodium Caplets, 220 are acceptable.

DISSOLUTION: The dissolution testing conducted on Naproxen Sodium Caplets and Tablets is acceptable. Waiver is granted for the tablet shaped Naproxen Sodium

PRIMARY REVIEWER: BRANCH: III

INITIAL: DATE: 1/11/96

BRANCH CHIEF: BRANCH:

INITIAL: DATE: 1/14/96

DIRECTOR
DIVISION OF BIOEQUIVALENCE

INITIAL: DATE: 1/31/96

DIRECTOR
OFFICE OF GENERIC DRUGS

INITIAL: N/A DATE:

ANDA 74-661

JAN 30 1996

Perrigo Company.
Attention: Elizabeth M. Pileggi.
117 Water Street
Allegan MI 49010

JAN 30 1996

Dear Madam:

Reference is made to your abbreviated new drug application dated April 24, 1995, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Naproxen Sodium Tablets/Caplets 220 mg.

The following comments pertain only to bioequivalency issues in the May 11, and December 14, 1995 submissions.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 900 mL of 0.1M phosphate buffer pH 7.4 at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

   Not less than of labeled amount of the drug in the dosage form is dissolved in 45 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

JAN 18 1996

Naproxen Sodium
220 mg Tablets/Caplets
ANDA # 74-661
Reviewer: Moheb H. Makary
WP 74661SDW.495

Perrigo Company
Allegan, Michigan
Submission Date:
April 24, 1995
May 11, 1995
December 14, 1995

Review of Bioequivalence Studies, Dissolution Data and Waiver Request

I. Objective:

The firm has submitted in vivo bioequivalence study reports of fasting and nonfasting studies on its naproxen sodium caplets, 220 mg and dissolution data to compare the test product with Hamilton's Aleve® 220 mg caplets. The formulations and the dissolution testing data for its test products the 220 mg Caplet and the 220 mg Tablet-shaped Naproxen Sodium were also submitted. The firm has requested a waiver of in vivo bioequivalence requirements for its Tablet-shaped naproxen sodium, 220 mg.

II. Background:

Naproxen sodium, 2-naphthaleneacetic acid, 6-methoxy-a-methyl sodium salt is a nonsteroidal anti-inflammatory drug with analgesic and antipyretic properties. It is rapidly and completely absorbed from the gastrointestinal tract. However, absorption can be delayed when taken with food. After administration of naproxen sodium, peak plasma levels of naproxen anion are attained at 1-2 hours with steady-state conditions normally achieved after 4-5 doses. The mean biological half-life of naproxen in human is approximately 13 hours. Approximately 95% of the dose is excreted in the urine, primarily as naproxen, 6-O-desmethyl naproxen or their conjugates. The rate of excretion has been found to coincide closely with the rate of drug disappearance from the plasma. The drug does not induce metabolizing enzymes.
Studies indicate that although total plasma concentration of naproxen in normal subjects is unchanged, the unbound plasma fraction of naproxen is increased in the elderly. Caution is advised when high doses are required and some adjustment of dosage may be required in elderly patients.
Naproxen sodium is indicated in the relief of mild to moderate pain and for the treatment of primary dysmenorrhea. It is also indicated for the treatment of rheumatoid arthritis, osteoarthritis, juvenile arthritis, ankylosing spondylitis, tendinitis and bursitis, and acute gout.

Naproxen sodium 220 mg tablet (Aleve®) is marketed by Hamilton Pharmaceuticals as an OTC drug product.

III. Study #116-02-10616 for single dose Fasting Bioequivalence Study:

Study site

Investigators:

Study design:	A randomized, single-dose, open-label, 2-way crossover bioequivalence study under fasting conditions.
Study date:	Period I December 27-31, 1994 Period II January 3-7, 1995
Subjects:	Twenty-six (26) male subjects were dosed period I, twenty-four (24) subjects completed the clinical portion of the study. The subjects were judged to be healthy based on medical history, physical examination and clinical laboratory tests, within 30 days prior to period 1 dosing. All subjects were within 18 to 45 years of age, and were within ± 15% of their IBW.
Exclusion criteria:	Consisted of: -Known history of hypersensitivity to naproxen sodium, ASA or any other non-steroidal anti-inflammatory drugs. -Known history or presence of cardiac, pulmonary, endocrine, neuromuscular, neurological, hematological, liver or kidney disease, or any condition known to interfere with the absorption, distribution, metabolism or excretion of drugs. -Known history of asthma, chronic bronchitis or other bronchospastic condition. -Active or recent history of inflammatory diseases of the gastrointestinal tract such as, gastritis, regional enteritis or ulcerative colitis.
Concurrent medication:	Subjects were informed not to take any prescription drugs for at least 14 days, or OTC medications for 7 days of the first drug administration. Subjects were requested to abstain from alcohol for 24 hours and xanthine-containing foods and fluids for 12 hours prior to each phase of the study.

Dose and treatment: All subjects completed an overnight fast (10 hours) before any of the following drug treatments:

Test product: A. 2x220 mg naproxen sodium caplets (Perrigo), lot #4X1042, lot size Caplets. Content uniformity and potency are 100.7% and 102.3%, respectively.

Reference product: B. 2x220 mg Aleve^{R} caplets (Hamilton Pharms), lot #4222Y, Exp. 7/97. Content uniformity and potency are 100.9% and 101.2%, respectively.

Food and fluid intake: Following drug administration, the subjects remained fasting for 5 hours and then received a meal. Standard meals or snacks were provided at appropriate times thereafter. Meal plans were identical for both periods.

Blood collection: Blood samples (1x10 mL) were taken prior to drug administration. Similarly, 1x10 mL samples were drawn at the following times after dosing: 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 36, 48 and 72 hours. Serum samples were separated and promptly frozen at -20^{o}C pending assay for naproxen.

Washout period: One week.

Assay Methodology:

Analytical Notes: Subjects 10 and 16 did not complete the entire clinical portion of the study. No results are reported for these two subjects. For subjects 13-2-15, 20-20-17, 24-1-17, and 24-2-15, no sample was present, and no results are reported.

Statistical Analysis:

AUC(0-t), AUCinf, Cmax, Kel, T1/2 and concentrations at each

sampling time point were determined. ANOVA was performed at alpha level of 0.05 using the GLM procedure of SAS. The 90% confidence intervals were calculated for parameters AUC (0-t), AUCinf and Cmax. The 90% confidence intervals were also calculated for LnAUC(0-t), LnAUCinf and LnCmax.

IV. In Vivo Results:

Twenty-six (26) male subjects were enrolled in the study, twenty-four successfully completed the study. Subject #10 failed to return to the facility to complete period II of the study. Subject #16 was withdrawn from the study prior to period II dosing for testing positive for ethyl alcohol. Subject #8 exhibited an extreme pharmacokinetic anomaly in phase I that was confirmed by reassay: the 72 hour sample was the peak concentration, while Cmax was expected to occur near to 1 hour after dosing. The subject admitted to take Aleve® for complaints of fever and muscle aches from December 30, 1994 until January 2, 1995. This information was not provided during the conduct of the study when the subject was questioned by the clinic staff. Consequently, the subject's serum concentrations were excluded from the data analysis. Four of the subjects experienced adverse events during the study (Table I). Subject #10 continued to exhibit an adverse events at discharge from the facility on period I. Follow-up with this subject did not return to the facility to complete the study. All other events were transient in nature and resolved spontaneously without medical intervention.

The serum concentrations and pharmacokinetic parameters for naproxen are summarized in Table II.

Table II

Mean Serum Naproxen Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 440 mg (2x220 mg Caplets) Naproxen Sodium Under Fasting Conditions

(N=23)

Time hr	Perrigo Test product Lot #4X1042 ug/mL (CV%)	Hamilton Reference Product Lot #4222Y ug/mL (CV%)
0	0	0
0.33	33.07 (73)	37.45 (61)
0.67	58.81 (37)	60.16 (23)
1	56.03 (31)	59.47 (20)
1.5	51.98 (21)	55.76 (24)
2	53.13 (19)	51.69 (12)
2.5	49.43 (16)	48.27 (17)
3	45.18 (13)	43.03 (15)
3.5	44.48 (17)	42.99 (15)
4	41.45 (13)	41.63 (19)
6	33.95 (16)	32.87 (15)
8	28.25 (14)	27.55 (16)
12	21.13 (19)	21.02 (19)
16	17.12 (24)	16.54 (19)
24	13.27 (26)	12.65 (21)
36	7.68 (25)	7.24 (20)
48	4.43 (40)	4.11 (48)
72	0.20 (469)	0.34 (325)

			Difference%	90% CI
AUC(0-t)(ug.hr/mL)	824.00(19)	806.60(18)	2.16	
AUCinf (ug.hr/mL)	943.10(18)	925.90(18)	1.86	
Cmax (ug/mL)	67.96(19)	67.87(21)	0.13	
Tmax (hr)	1.18(68)	1.04(59)		
Kel (1/hr)	0.0419	0.0420		
T1/2 (hr)	16.94	17.17		
LnAUC				98.4-105.4%
LnAUCinf				97.8-105.5%
LnCmax				93.1-108.1%

1. For Perrigo's test product, the mean AUC(0-t), AUCinf and Cmax values were 2.16%, 1.86% and 0.13% higher, respectively, than the reference product values. The differences were not statistically significant. The 90% confidence intervals are within the acceptable range of 80-125%. The reviewer's calculations are in agreement to those submitted by the firm.
2. The plasma naproxen levels peaked at 0.67 hour for both the test and reference products, which is in agreement with the literature reported values for the reference product (Goodman and

Gilman's The Pharmacological Basis of Therapeutics, 8th edition, p.666, 1990).

3. There were six samples obtained at times that deviated from the scheduled time. In each of these instances, the AUC(0-t) was calculated using the actual time to determine whether it would differ appreciably from the AUC calculated using the scheduled time. The differences in calculated AUCs were all less than 1%.

V. Study #116-03-10617 For a Single-Dose Bioequivalence Study Under Fasting and Nonfasting Conditions:

The objective of this study is to compare the bioavailability of Perrigo's naproxen sodium 220 mg caplets with Hamilton's Aleve® 220 mg caplets under fasting and nonfasting conditions.

Study site:

Investigators: Same as Study #116-02-10616 above

Study design: Single-dose, randomized, open-label, 3-way crossover bioavailability study under fasting and nonfasting conditions.

Study date: Period I January 19-23, 1995
Period II January 26-30, 1995
Period III February 2-6, 1995

Subjects: Eighteen (18) healthy male subjects enrolled and completed the study.

Exclusion criteria& Concurrent medication: Same as Study #116-02-10616 above

Dose and treatment:

A. 2x220 mg naproxen sodium caplets (Perrigo), lot #4X1042, following a standardized breakfast.

B. 2x220 mg Aleve® caplets (Hamilton), lot #4222Y, following a standardized breakfast.

C. 2x220 mg naproxen sodium caplets (Perrigo), lot #4X1042, following 10 hours overnight fast.

Food and fluid intake: Subjects on regimen A and B fasted for 10 hours before a standard breakfast. The breakfast consisted of 240 mL of whole milk, one fried egg, one slice of Canadian bacon,

one slice of American cheese, one buttered English muffin and 180 mL of orange juice served 30 minutes prior to drug administration. Meals or snacks were served at 5 hours after dosing and at appropriate times thereafter. Subjects on regimen C fasted for 10 hours before dosing and 5 hours after dosing. Water was permitted ad lib until 1 hour before dosing and at 1 hour after dosing.

Blood collection: Same as Study #116-02-10616 above

Washout period: One week

Assay Methodology: Same as Study #116-02-10616 above.

Analytical Notes:

2. During the clinical portion of the study, no samples were collected for subject 1, phase I, draw 17 and subject 5, phase I, draw 16. No analytical data reported for these samples.
3. Of the 970 samples assayed for this study, 12 samples were reassayed.

Statistical Analysis:

AUC(0-t), AUCinf, Cmax, Kel, T1/2 and concentrations at each sampling time point were determined. ANOVA was performed using the GLM procedure of SAS.

VI. In Vivo Results:

Eighteen (18) healthy male subjects were enrolled and completed the study. The serum samples from the 18 subjects were assayed for naproxen. Subject #15 experienced lump on neck (January 27, 1995). The event was thought to have no relationship to the study medication. The event remained unresolved at discharge from the study. Continued follow-up with the subject was attempted, but proved to be unsuccessful.

The serum concentrations and pharmacokinetic parameters of naproxen are summarized in Table III.

Table III

Mean Serum Naproxen Concentrations and Pharmacokinetic Parameters Following an Oral Dose of 440 mg Naproxen Sodium (2x220 mg) Caplets Under Fasting and Nonfasting Conditions
(N=18)

Time hr	Treatment A Perrigo Lot #4X1042 Nonfasting ug/mL (CV%)	Treatment B Hamilton Lot #4222Y Nonfasting ug/mL (CV%)	Treatment C Perrigo Lot #4X1042 Fasting ug/mL (CV%)
0	0	0	0.56 (424)
0.33	5.18 (146)	3.78 (219)	38.99 (57)
0.67	21.61 (73)	14.29 (127)	68.96 (24)
1	35.20 (54)	25.47 (76)	68.08 (15)
1.5	45.10 (43)	36.68 (50)	66.20 (8)
2.0	49.71 (25)	45.80 (37)	62.28 (12)
2.5	57.44 (12)	48.95 (26)	56.15 (14)
3.0	53.51 (13)	50.77 (20)	54.56 (13)
3.5	53.47 (11)	52.81 (15)	50.43 (12)
4	51.44 (13)	50.69 (16)	47.58 (14)
6	44.63 (12)	44.86 (14)	41.98 (13)
8	36.53 (12)	35.94 (11)	34.83 (12)
12	27.96 (13)	27.66 (12)	26.42 (12)
16	22.13 (15)	22.02 (11)	21.67 (15)
24	17.52 (19)	17.63 (15)	17.03 (16)
36	10.32 (27)	9.99 (24)	10.06 (23)
48	6.56 (32)	6.32 (29)	6.61(21)
72	1.54 (152)	1.15 (173)	0.92 (197)

				A/B
AUC(0-t) (ug.hr/mL)	1052.6(19)	1013.3(16)	1052.0(15)	1.04
AUCinf (ug.hr/mL)	1183.1(19)	1143.9(17)	1199.0(16)	1.03
Cmax (ug/mL)	62.1(10)	59.0(16)	76.6(9)	1.05
Tmax (hr)	2.4(34)	3.1(44)	0.97(41)	
Kel(1/hr)	0.0404	0.0412	0.0396	
T1/2(hr)	17.75	17.41	17.93	

1. For Perrigo's Naproxen sodium, the mean AUC(0-t), AUCinf and Cmax values were 3.88%, 3.4%, and 5.25% higher, respectively, than the reference product values under nonfasting conditions. The ratios of the test mean to the reference mean are within the acceptable range of 0.8-1.2 for AUC(0-t), AUCinf and Cmax.

2. The naproxen serum levels peaked at 2.5 and 3.5 hours for the test and reference products, respectively, under nonfasting conditions and at 0.67 hour for the test product under fasting conditions.

3. The mean Cmax value after dosing with food was about 19% lower than when dosing was in the fasted state. Also, the Tmax delayed about 1.5 hours.

4. There were significant period differences for AUC(0-t)and AUCinf. Since the within subject variance is very small for this drug (C.V. less than 5%), these period differences could be significant.

5. A significant sequence effect was observed for AUC(0-t) and Cmax. Additional statistical analysis to test for carry-over effects, showed no evidence of inequality. Because the study meets the criteria according to The Guidance "Statistical Procedures of Bioequivalence Studies Using a Standard Two Treatments Crossover Design" and the lack of evidence for unequal carry-over effects, the study is valid to assess the bioequivalence of naproxen sodium under fasting and nonfasting conditions.

6. Subject #1 had a predose naproxen concentration of 10.1 ug/mL in period III (under fasting conditions). This value is higher than the period II, 72 hours postdose concentration of 3.57 ug/mL. When the subject was asked during the study, the subject denied taking over the counter naproxen sodium during the washout period following phase II. Excluding this subject from the statistical analysis has no effect on the outcome of the study.

VII. In Vitro Dissolution Testing:

Method:	USP 23 apparatus II (paddle) at 50 rpm
Medium:	900 mL phosphate (pH 7.4) at 37°C
Number of Tablets:	12
Test products:	Naproxen Sodium (Perrigo), 220 mg caplet, lot #4X1042.
	Naproxen Sodium (Perrigo), 220 mg tablet, lot #4W1043.
Reference product:	Aleve® (Hamilton), 220 mg caplet, lot #4222Y
Specification:	NLT in 45 minutes.

The dissolution testing results are given in Table IV.

VIII. Formulations:

Perrigo's formulation for its naproxen sodium 220 mg caplet or tablet is given below:

Components	MG/Caplet or Tablet
Carnauba Wax NF Magnesium Stearate NF Microcrystalline Cellulose Naproxen Sodium USP	220.00 mg
Povidone USP Purified Water USP Talc USP	-
Total Weight	313.15 mg

IX. Comments:

1. The firm's in vivo bioequivalence studies under fasting and nonfasting conditions using 220 mg naproxen sodium caplet are acceptable. Under nonfasting conditions, Cmax seems to be decreased and Tmax is delayed. The test product is judged to be comparable in both rate and extent of absorption to the reference product. The 90% confidence intervals for LnAUC(0-t), LnAUCinf and LnCmax are within the acceptable range of 80-125%.

2. The in vitro dissolution testing for the test products 220 mg naproxen sodiun caplet and shaped tablet is acceptable.

3. The components and composition for naproxen sodium 220 mg both the tablets and caplets are exactly the same.

4. Waiver of in vivo study requirements may be granted for the Tablet shaped naproxen sodium, 220 mg.

X. Recommendations:

1. The bioequivalence studies under fasting and nonfasting conditions conducted by Perrigo Company, on its Naproxen Sodium 220 mg caplet, lot #4X1042, comparing it to Hamilton's Aleve® 220 mg caplet, have been found to be acceptable by the Division of Bioequivalence. The studies demonstrated that Perrigo's Naproxen Sodium 220 mg caplet is bioequivalent to the reference product, Aleve® 220 mg Caplet, manufactured by Hamilton Pharmaceuticals.

2. The dissolution testing conducted by Perrigo, on its Naproxen Sodium Caplet and Tablet, 220 mg, lots #4X1042 and #4W1043, respectively, is acceptable. The formulation for the 220 mg shaped tablet is identical to the 220 mg caplet which underwent acceptable bioequivalence testing. Waiver of in vivo bioequivalence study requirements for the table shaped naproxen sodium, 220 mg of the test product is granted. The Division of Bioequivalence deems Naproxen Sodium 220 mg Tablet, manufactured by Perrigo Company, to be bioequivalent to Aleve® 220 mg Tablet manufactured by Hamilton Pharmaceuticals.

3. The dissolution testing should be incorporated into the firm's

manufacturing controls and stability program of the firm. The dissolution testing should be conducted in 900 mL of 0.1M phosphate buffer pH 7.4 at 37°C using USP 23 apparatus II (paddle) at 50 rpm. The test product should meet the following specification:

> Not less than of labeled amount of the drug in the dosage form is dissolved in 45 minutes.

4. From the bioequivalence point of view, the firm has met the requirements of the in vivo bioequivalence and the in vitro dissolution testing.

The firm should be informed of the above recommendations.

Moheb H. Makary, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Date: 1/16/96

Concur _____ Date: 1/18/96
Keith Chan, Ph.D.
Director
Division of Bioequivalence

MMakary/1-11-96 wp 74661SDW.495
cc: ANDA #74-661, original, HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-658 (Mhatre, Makary), Drug File, Division File.

Table IV In Vitro Dissolution Testing

Drug (Generic Name): Naproxen Sodium Tablet/Caplet
Dose Strength: 220 mg
ANDA No.: 74-661
Firm: Perrigo Company
Submission Date: April 24, 1995
File Name: 74661SDW.495

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 900 mL of 0.1M phosphate buffer pH 7.4
Specifications: NLT in 45 minutes
Reference Drug: Aleve
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 4X1042 Caplet Strength(mg) 220			Reference Product Lot # 4222Y Caplet Strength(mg) 220		
	Mean %	Range	%CV	Mean %	Range	%CV
15	75		11.8	78		13.3
30	100		3.5	97		4.3
45	102		1.5	98		3.2
60	102		1.2	98		2.6

Sampling Times (Minutes)	Test Product Lot # 4W1043 Tablet Strength(mg) 220			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV
15	73		10.1			
30	100		4.2			
45	102		1.9			
60	102		1.3			

Table I

TABLE 5: ADVERSE EVENTS
NAPROXEN SODIUM TABLETS
#116-02-10616

SUBJECT#	DATE	TIME	EVENT	SEVERITY	RESOLUTION	RELATIONSHIP TO DRUG	Rx	PRODUCT UNDER STUDY
7	12/28/94	0930	Tired	Mild	12/28/94 1930	Possible	None	Hamilton
8	12/30/94	Unknown	Flu symptoms	Mild	01/02/95	None	**	Perrigo
10	12/28/94	0630	Sore throat	Mild	12/28/94 2330	None	*	None
	12/28/94	Predose	Sores on gums	Mild	Unresolved at discharge	None	None	None
21	12/28/94	0730	Headache	Mild	12/28/94 0930	None	None	None

* - Warm saltwater gargle.
** - Self administered Aleve® on 12/30/94 through 01/02/95.

3 15

DRUG LEVELS

ANALYTICAL SUMMARY

STATISTICAL SUMMARY

Figure 1: Mean Naproxen Serum Levels

n = 23

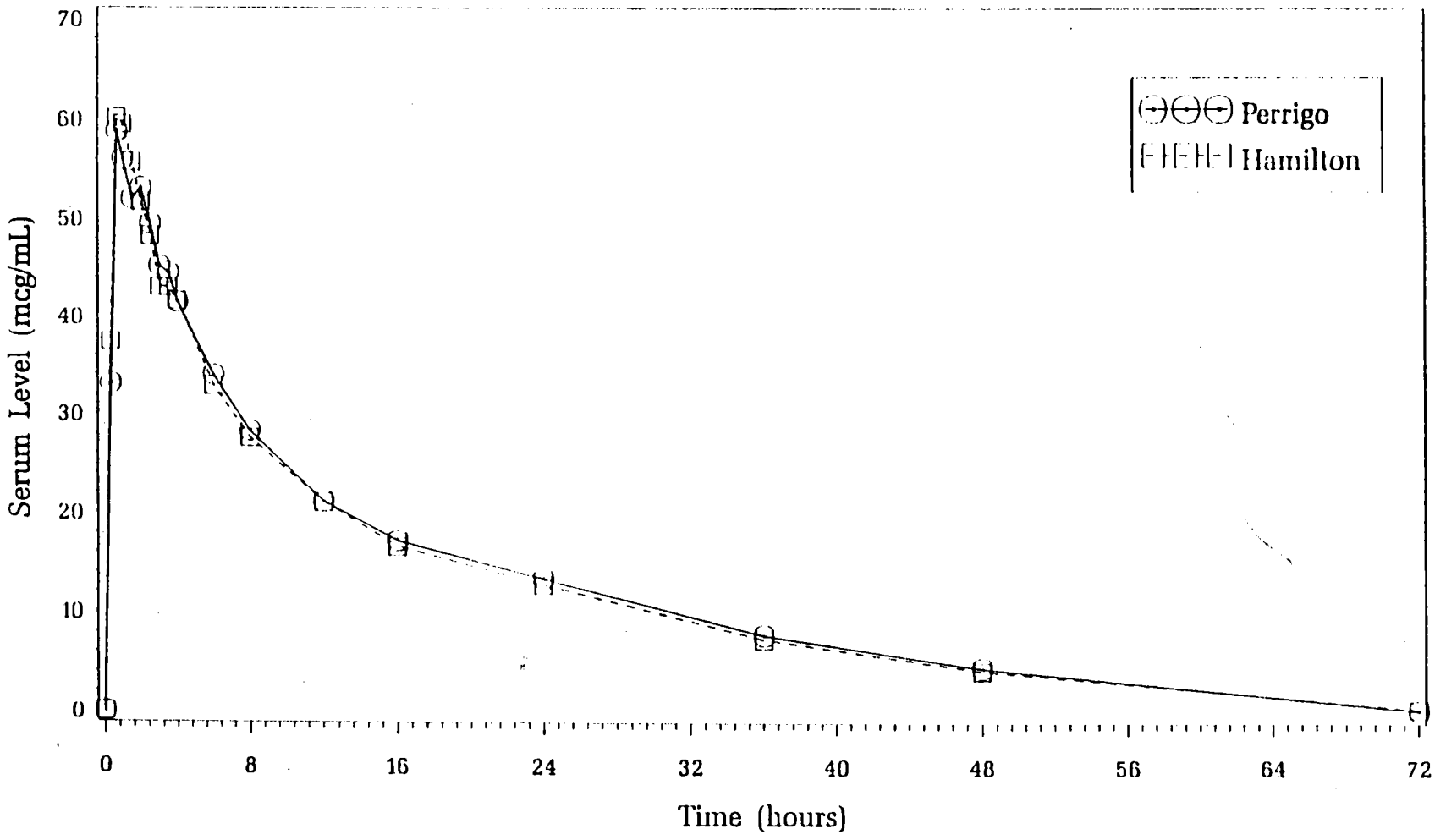


Figure 1: Mean Naproxen Serum Levels

n = 18